Received: 28 June 2021 | Revised: 30 September 2021 | Accepted: 19 October 2021

DOI: 10.1002/rth2.12624

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

# Comparison of 4F-PCC in obese and nonobese patients with life-threatening bleeding or requiring emergent surgery

Jessica Rimsans PharmD, BCPS[1] | Karen Berger PharmD, FASHP, FCCM, BCPS, BCCCP[2] | Sarah Culbreth PharmD, BCPS[1] | Christopher Hood PharmD, MBA[3] | Katleen Chester PharmD[4] | Jean M. Connors MD[5] | Laurel Omert MD[6]

[1]Department of Pharmacy Services, Brigham and Women's Hospital, Boston, Massachusetts, USA

[2]Department of Pharmacy, NewYork-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York, USA

[3]Medical Affairs, CSL Behring, King of Prussia, Pennsylvania, USA

[4]Department of Pharmacy, Grady Memorial Hospital, Atlanta, Georgia, USA

[5]Division of Hematology, Brigham and Women's Hospital, Boston, Massachusetts, USA

[6]Hemanext Inc, Lexington, Massachusetts, USA

**Correspondence**
Jessica Rimsans, Department of Pharmacy Services, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
Email: jrimsans@bwh.harvard.edu

**Handling Editor:** Dr Johnny Mahlangu

## Abstract

**Background:** Four-factor prothrombin complex concentrate (4F-PCC) dosing is based on INR and actual body weight (ABW), with maximum doses not to exceed the dose used in patients weighing >100 kg (Kcentra PI). There are limited data comparing the efficacy of 4F-PCC between patients with low body weight ≤100 kg (LoWT) and high body weight >100 kg (HiWT).

**Methods:** We conducted a retrospective cohort study of patients on warfarin who received 4F-PCC for life-threatening major bleeding or requiring emergent surgery between January 2015 to June 2018 at three academic medical centers. These data were combined with a dataset from 2 randomized Phase 3b clinical trials.

**Results:** We included 388 patients who received 4F-PCC, 318 (82%) were LoWT, and 70 (18%) were HiWT. Indication for 4F-PCC for life-threatening bleeding and emergent surgery was 266 (69%) and 122 (31%) patients, respectively. The most common bleeding type was intracranial hemorrhage (41%), followed by gastrointestinal (36%). The median dose was 2283 units (25 units/kg), and 2.1% of patients required a repeat dose.

**Conclusion:** In those >100 kg, we found no difference in achieving international normalized ratio (INR) ≤1.3, hemostasis in intracranial hemorrhage, or thrombosis. In-hospital mortality occurred 15% in LoWt versus 6% in HiWT (CI 1.8%–17%, $p = 0.034$). Achievement of INR ≤ 1.5 was significantly lower in the LoWT group compared to the HiWT group (80% versus 91%, CI −20% to −2.5%, $p = 0.03$).

KEYWORDS
anticoagulation, bodyweight, obesity, prothrombin complex concentrate, warfarin

**Essentials**

- The efficacy of four-factor prothrombin complex concentrate for warfarin reversal in patients weighing >100 kg is not well established.
- Package insert dosing guidelines recommend a maximum dose based on 100 kg.
- In those >100 kg, we found no difference in achieving international normalized ratio (INR) ≤1.3, hemostasis in intracranial hemorrhage, or thrombosis.
- A capped dose for patients >100 kg achieves INR ≤1.5 in 91%.

## 1 | INTRODUCTION

Four-factor prothrombin complex concentrate (4F-PCC) was approved by the US Food and Drug Administration for warfarin reversal in adult patients with acute major bleeding or those requiring an urgent surgery or invasive procedure in 2013. Dosing is based on the international normalized ratio (INR) and actual bodyweight (ABW), with maximum doses not to exceed the dose used in patients weighing >100 kg.[1] This dosing strategy is applicable to all patients regardless of weight or body mass index (BMI). It has been observed that blood volume increases with bodyweight in a nonlinear fashion in obese patients; hence, it is difficult to speculate whether capping the dose would be effective at achieving the desired INR target.[2] Alternative dosing strategies have been suggested, but evidence remains uncertain, particularly in the obese population.[3-9]

Currently, there are no published data comparing the efficacy of 4F-PCC between patients with low bodyweight (LoWT; ≤100 kg) and high bodyweight (HiWT; >100 kg). The aim of this study was to compare the achievement of INR normalization (INR ≤1.3), hemostasis, thrombosis, and in-hospital mortality between patients with LoWT and patients with HiWT.

## 2 | METHODS

This was a multicenter, retrospective cohort study of patients on warfarin who received 4F-PCC between January 2015 and June 2018, for life-threatening major bleeding or requiring emergent surgery. The study was performed at three academic medical centers, which included NewYork–Presbyterian Hospital/Weill Cornell Medical Center, Grady Memorial Hospital, and Brigham and Women's Hospital. Institutional review board approval was obtained from all three sites before study initiation. Data were standardized and collected from the electronic medical record at each institution, then combined with data from two previously published prospective, randomized phase 3b studies (clinical trial data) that met inclusion criteria.[10,11] The three medical center data cohort is referred to as the nonclinical trial data, and the phase 3b is referred to as the clinical trial data.

We included patients who were >18 years of age, receiving warfarin with a presenting INR >1.5, and experiencing life-threatening major bleeding or requiring emergent surgery. The INR for inclusion in the clinical trial data was >2 drawn within 3 hours of 4F-PCC administration.[10,11] Patients who were HiWT received the dose cap as per package insert, for the specified INR range.[1] We excluded patients if the presenting INR was ≤1.5 before administration of 4F-PCC, if they did not have an INR rechecked within 12 hours of 4F-PCC, and patients who received 4F-PCC for indications other than reversal of warfarin-associated major bleeding or requiring emergent surgery. In contrast to the clinical trial data, the nonclinical trial data did not exclude patients with Glasgow Coma Scale score <7, intracranial hemorrhage (ICH) volume >30 mL, subdural hematoma >10 mm thickness, midline shift >5 mm, hydrocephalus with subarachnoid hemorrhage, infratentorial location, or intraventricular extension as noted in Sarode et al.[10] Other data points collected included dose of 4F-PCC, INR, site of bleeding, type of surgery, administration of plasma and vitamin K, time to first repeat INR post 4F-PCC administration, the need for redosing of 4F-PCC or other concentrated clotting factors, hemostasis, thrombotic events within 7 days, and mortality.

### 2.1 | Outcomes

The primary outcome of the analysis was an achievement of an INR ≤1.3. Secondary outcomes included achievement of INR ≤1.5, hemostasis, thrombotic events and in-hospital mortality. Warfarin reversal was assessed by a decrease in the posttreatment INR (within 12 hours of 4F-PCC administration) compared to the pretreatment INR. The INR goals were selected to allow for comparison between previously published literature evaluating reversal effect.

Definitions for hemostasis differed for patients included in the nonclinical data versus the clinical trial data. Hemostasis for the nonclinical trial cohort was defined as follows: ICH: first neuroimaging result within 24 hours of 4F-PCC administration demonstrating no change, or an improvement in hematoma volume; other major bleeding including gastrointestinal bleeding (GIB): hemoglobin (Hgb) decrease of ≤20% from baseline within 24 hours of 4F-PCC administration; surgery: Hgb decrease of ≤20% from baseline within 24 hours, and no supplemental blood products containing coagulation factors (eg, 4F-PCC) were given intraoperatively after 4F-PCC administration. The criteria used to define hemostasis in the clinical trial data are previously reported and have been modified for data collection purposes.[10,11]

Thrombotic events from the clinical trial data (adjudicated to 7 days for this analysis) and nonclinical trial cohort were included if they occurred within 7 days of 4F-PCC administration to standardize data collection among institutions. Events were included if they

were documented in the electronic health record and were confirmed by computed tomography (CT) and/or Doppler ultrasound demonstrating evidence of deep vein thrombosis (DVT), pulmonary embolism, stroke or transient ischemic attack, myocardial infarction (MI), and arterial events.

### 2.2 | Statistical analysis

Data from the three hospitals that comprised the nonclinical trial cohort were combined with the clinical trial cohort and standardized according to predefined end points. Statistical analysis was performed by an independent biostatistician. To compare quantitative data between the two weight categories, either the two-sample *t* test or the Wilcoxon rank-sum test was used depending on the data distribution. To evaluate categorical data, the chi-square test for goodness of fit was employed. If there were small expected cell sizes (<5), then an exact calculation of the *P* value was employed (StatXact 12.0, Cytel Inc., Cambridge, MA, USA). All significance tests employed a 5% level of significance. Confidence intervals were calculated using either the standard *t* distribution approach for quantitative data and the Wald-z or exact binomial approach for categorical data.

## 3 | RESULTS

From January 2015 to June 2018, 388 patients were identified, with 211 patients from the nonclinical trial cohort and 177 patients from clinical trial cohort (Figure 1). Of the 388 patients, 318 (82%) were LoWT and 70 (18%) were HiWT. Patient baseline characteristics are noted in Table 1. Groups were similar with the exception of the weight-associated variables (weight in kilograms, BMI), total 4F-PCC dose in units, age, and time to repeat INR. Presenting INR and indication for reversal were not statistically significant between groups. The median weight and BMI were 74.3 kg (interquartile range [IQR], 65-84 kg) and 25.9 kg/m$^2$ (IQR, 22.6-28.7 kg/m$^2$) in the LoWT group, and 109.5 kg (IQR, 102-123 kg) and 37.0 kg/m$^2$ (IQR, 34.5-43.1 kg/m$^2$) in HiWT group. There was no difference in the administration of vitamin K or fresh frozen plasm after 4F-PCC dose between groups.

[1]4F-PCC was indicated for life-threatening bleeding and emergent surgery in 266 (68.6%) and 122 (31.4%) patients, respectively (Table 1). The most common bleeding site was ICH, which occurred in 109 patients (41%), followed by gastrointestinal (GI) hemorrhage 95 (36%). Other sites of bleeding occurred in 62 (23%) patients and were considered non-GI and non-ICH. Of those patients who were reversed for emergent surgery, the most common indication was before an invasive procedure such as a central line placement, paracentesis, or a bronchoscopy in 62 patients (51%) followed by GI procedures in 27 (22%) patients and orthopedic procedures in 23 (19%) patients. See Table 2 for full results.

Overall, achievement of the primary outcome of INR reduction to ≤1.3 occurred in 64% of patients and was not statistically different between groups (65% LoWT vs 63% HiWT group; $P = .80$). Time from administration of 4F-PCC to repeat INR was longer in the HiWT group (73 minutes vs 45 minutes; $P = .02$) (Figure 2). Secondarily, INR reduction to ≤1.5 was achieved in 82% overall. More patients in the HiWT group had INR reduction to ≤1.5 (80% LoWT vs 91% HiWT; $P = .03$).

Hemostasis in bleeding patients was achieved in 64% compared to 78% in the surgical patients. There were more HiWT bleeding patients who achieved hemostasis (60% LoWT vs 82% HiWT; $P = .004$), with no difference observed in surgical hemostasis (77% LoWT vs 80% HiWT; $P = .77$; Table 2, Figure 3). Hemostasis for those with ICH was achieved in 70 (72.9%) patients (73% LoWT vs 85% HIWT; $P = .51$). In those who failed to achieve hemostasis in the LoWT ICH nonclinical trial group, 84% achieved an INR ≤1.3, 95% achieved INR reduction to ≤1.5, and 24% had expansion on repeat head CT after receiving 4F-PCC. In patients in the HiWT nonclinical trial cohort, 60% achieved an INR ≤1.3, and 93% achieved an INR ≤1.5. Two patients with ICH (16.6%) had documented evidence of expansion despite both achieving INR reduction of ≤1.3 and ≤1.5. Although data from the clinical trial cohort included hemostasis and expansion of ICH on imaging, individual patient data are not available.

In patients with GI bleeding, 49% achieved hemostasis in the LoWT group compared with 89% in the HiWT group ($P = .003$). All other sites of bleeding (non-GI and non-ICH) were not statistically significant between groups in rates of achievement of hemostasis (50% LoWT vs 79% HiWT; $P = .07$). In those requiring 4F-PCC for emergent surgery, there was no difference between groups in achievement of hemostasis ($P = .77$; Table 2).

Specifically, when looking at the nonclinical trial cohort, 80% of ICH patients in the LoWT group achieved an INR of ≤1.3, and 93% achieved an INR of ≤1.5 with 78% achieving hemostasis. For the HiWT group: 54% achieved an INR of ≤1.3 and 100% achieved an INR of ≤1.5, and 83.3% achieved hemostasis. The median time to repeat INR in the LoWT group was 124 minutes (IQR, 67.8-270 min) versus a median of 133 minutes (IQR, 73.3-217.5 minutes) in the

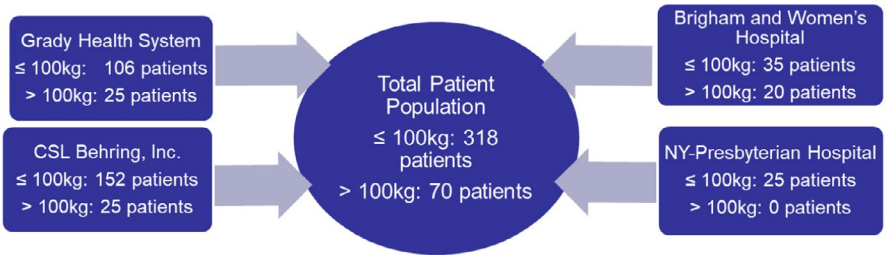


**FIGURE 1** Patient inclusion

**TABLE 1** Baseline demographics

| | Total (n = 388) | Weight ≤100 kg LoWT (n = 318) | Weight >100 kg HiWT (n = 70) | *P* value |
|---|---|---|---|---|
| Retrospective data (patients, n) | 211 | 166 | 45 | 0.07 |
| Phase 3b data (patients, n) | 177 | 152 | 25 | – |
| Male, n (%) | 208 (53.6) | 167 (52.5) | 41 (58.6) | 0.36 |
| Age, y, average ± SD | 69.4 ± 14.08 | 70.0 ± 14.52 | 66.7 ± 11.61 | .014 |
| Weight, kg, median, IQR | 71.0<br>67.6-94.3 | 74.3<br>65.0-84.0 | 109.5<br>102.0-123.0 | <.0001 |
| BMI, median, IQR | 26.9<br>23.7-31.7 | 25.9<br>22.6-28.7 | 37.0<br>34.5-43.1 | <0.0001 |
| Indication of 4F-PCC | | | | |
| Bleed, n (%) | 266 (68.6) | 221 (69.5) | 45 (64.3) | .40 |
| Surgery, n (%) | 122 (31.4) | 97 (30.5) | 25 (35.7) | |
| Bleed location, n (%) | | | | |
| ICH | 109 (41.0) | 96 (34.8) | 13 (40.0) | .16 |
| GI | 95 (35.7) | 77 (43.4) | 18 (28.9) | |
| All other (non-GI, non-ICH) | 62 (23.3) | 48 (21.7) | 14 (31.1) | |
| Type of surgery, n (%) | | | | |
| Cranial/Neurosurgical | 4 (3.3) | 4 (3.3) | 0 (0) | .91 |
| Cardiothoracic | 6 (4.9) | 5 (5.2) | 1 (4.0) | |
| GI | 27 (22.1) | 20 (20.6) | 7 (28.0) | |
| Orthopedic | 23 (18.9) | 18 (18.6) | 5 (20.0) | |
| Invasive | 62 (50.8) | 50 (51.6) | 12 (48.0) | |
| Vitamin K, n (%) | 253 (65.7) | 209 (66.4) | 44 (62.9) | 0.58 |
| Fresh frozen plasma, n (%) postdose | 25 (6.4) | 22 (6.9) | 3 (4.3) | .59 |
| Total 4F-PCC initial dose (units) | | | | |
| Median, IQR | 2283<br>1900.52868.5 | 2132<br>17612615 | 2767<br>25003500 | <.0001 |
| Weight-based initial dose (unit/kg) | | | | |
| Median, IQR | 25<br>25-35 | 25<br>25-35 | 25<br>23-29.5 | |
| Predose INR, median, IQR | 3.20<br>2.4-4.9 | 3.21<br>2.4-4.9 | 3.03<br>2.3-4.8 | 0.3640 |
| Time to repeat INR, min, median, IQR | 49<br>32-145 | 45<br>31-134 | 73<br>41-161 | 0.02 |
| Required a repeat dose of 4F-PCC, n (%) | 8 (2.1) | 6 (1.9) | 2 (2.9) | .64 |

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; BMI, body mass index; GI, gastrointestinal; HiWT, high bodyweight; ICH, intracranial hemorrhage; INR, international normalized ratio; IQR, interquartile range; LoWT, low bodyweight.

[a]Surgery type GI from supplemental data only. Surgery type Other from 3003 data only, includes GI.

HiWT group. Repeat dosing was given in 6 (1.9%) in the LoWT group compared to 2 (2.9%) in the HiWT group (*P* = .64).

Thrombotic events within seven days after 4F-PCC occurred in 35 (9%) patients. There was no difference in the rate of thrombotic events between groups (9% LoWT vs 11% HiWT; *P* = .44; CI, 11.9%-6.0%; Table 2). In the LoWT group, there were 27 events (9%): 10 lower-extremity DVTs, 2 upper-extremity DVTs, 4 cerebrovascular accidents (CVAs), 3 line-associated thromboses, 7 superficial thromboses, and 1 MI. For those in the HiWT group, there were 8 events (11%): 4 lower-extremity DVTs, 1 CVA, 1 superficial thrombosis, and 2 MIs. No additional information regarding these events were collected and reinitiation of anticoagulation was not available. In-hospital mortality occurred in 15.1% of LoWT patients compared to 5.7% in the HiWT group (CI, 1.8%-17%; *P* = .03). Due to a small sample size, we were unable to perform a multivariate regression analysis or provide adequate statistical interpretation of regression models regarding other weight groups and hemostasis. Based on this, we found that bodyweight ≤100 kg in a patient who had ICH or did not achieve hemostasis were independent predictors of mortality.

**TABLE 2** Primary and secondary outcomes

| Outcome | Total (n = 388) | Weight ≤100 kg LoWT (n = 318) | Weight >100 kg HiWT (n = 70) | *P* value | CI, % |
|---|---|---|---|---|---|
| INR ≤1.3, n (%) | 249 (64.2) | 205 (64.5) | 44 (62.9) | .80 | −11.8 to 15.0 |
| INR ≤1.5, n (%) | 319 (82.2) | 255 (80.2) | 64 (91.4) | .03 | −20.0 to −2.5 |
| Hemostasis achieved per definition sheet (different for ICH bleed, vs other bleed and surgery). | | | | | |
| Bleeding patients, n (%) | | | | | |
| Overall | 169/266 (63.5) | 132/221 (59.7) | 37/45 (82.2) | .004 | −36.7 to −8.2 |
| ICH | 81/109 (74.3) | 70/96 (72.9) | 11/13 (84.6) | .508 | |
| GI | 54/95 (56.8) | 38/77 (49.4) | 16/18 (88.9) | .003 | |
| Non-GI, non-ICH | 35/62 (56.5) | 24/48 (50.0) | 11/14 (78.6) | 0.072 | |
| Surgical patients | | | | | |
| Overall | 95/122 (77.9) | 75/97 (77.3) | 20/25 (80.0) | .77 | −19.8 to 29.5 |
| Cranial/Neurosurgical | 1/4 (25.0) | 1/4 (25.0) | 0/0 | ... | |
| Cardiothoracic | 5/6 (83.3) | 4/5 (80.0) | 1/1 (100.0) | 1.0 | |
| GI | 23/27 (85.2) | 16/20 (80.0) | 7/7 (100.0) | .55 | |
| Orthopedic | 17/23 (73.9) | 14/18 (77.9) | 3/5 (60.0) | 0.58 | |
| Invasive | 49/62 (70.0) | 40/50 (80.0) | 9/12 (75.0) | .70 | |
| Thrombotic events, n (%) | 35 (9) | 27 (8.5) | 8 (11.4) | .44 | −11.9 to 6.0 |
| DVT (lower extremity) | 14 (3.6%) | 10 (3.1%) | 4 (5.7) | .29 | −11.7 to 2.2 |
| DVT (upper extremity) | 2 (0.5%) | 2 (0.6%) | 0 | 1.00 | −5.9 to 2.5 |
| CVA | 5 (1.3) | 4 (1.3) | 1 (1.4) | 1.00 | −7.6 to 2.4 |
| Line assoc. | 3 (0.8) | 3 (0.9) | 0 | 1.00 | −5.6 to 3.0 |
| Other (superficial) | 8 (2.1) | 7 (2.2) | 1 (1.4) | 1.00 | −6.7% to 3.6% |
| MI | 3 (0.8) | 1 (0.3) | 2 (2.9) | .08 | −10.6 to 0.4 |
| Mortality | 52 (13.4) | 48 (15.1) | 4 (5.7) | .03 | 1.8 to 17 |

*Note:* Confidence intervals are defined in terms of the difference in proportions ($p_{LO}$−$p_{HI}$). The Wald-z approach was used for all of the intervals except the thrombotic events where the Wilson score method was used.

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; GI, gastrointestinal; HiWT, high bodyweight; ICH, intracranial hemorrhage; INR, international normalized ratio; LoWT, low bodyweight; MI, myocardial infarction.

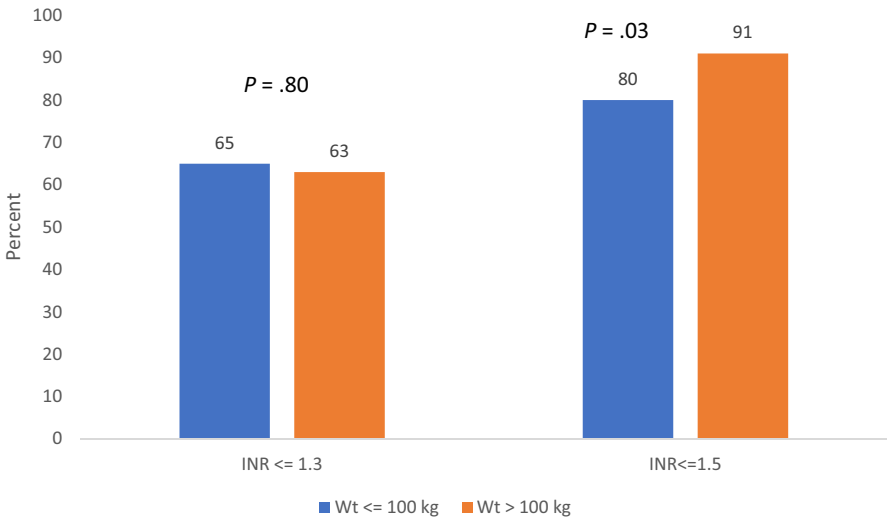


**FIGURE 2** Primary outcome: achievement of INR normalization. INR, international normalized ratio

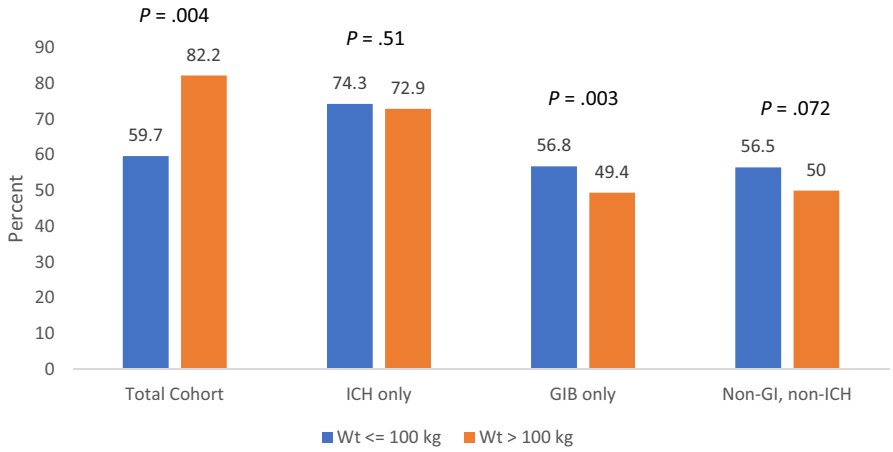


**FIGURE 3** Achievement of hemostasis. GI, gastrointestinal; GIB, gastrointestinal bleeding; ICH, intercranial hemorrhage

## 4 | DISCUSSION

In this cohort of 388 patients, we observed no difference in achievement of INR ≤1.3, or thrombotic events between patients <100 kg or >100 kg. Achievement of INR ≤1.5 was significantly higher in the HiWT group, with fewer patients experiencing in-hospital mortality ($P$ = .03). Anticoagulation reversal in the obese population has remained a question of interest. It was previously reported that vitamin K and plasma had no difference in reversal based on bodyweight.[12] One study reported that 70% of obese patients (BMI, 37.3 kg/m$^2$) achieved either partial or complete INR reversal (complete reversal <1.5, or partial <2.0) by 72 hours compared to 69% in nonobese patients, and failures were thought not to be associated with obesity and more so to their long time frame for INR collection of 72 hours.[12]

The optimal 4F-PCC dosing strategy that is both safe and efficacious in the obese population also remains in question. As blood volume does not increase proportionately with BMI, one may hypothesize that plasma coagulation factors, their effect on INR, and prothrombin complex concentrate (PCC) dosing should not be different between obese and nonobese patients. However, it has been documented that obese patients have an increased volume of distribution for drugs along with differences in their baseline coagulation and hemostatic systems.[13,14] Very limited evidence from the two 4F-PCC clinical trials documents reversal failure of 4F-PCC in patients who weigh >100 kg (obese).[10,11]

Smetana and colleagues observed that using actual body weight (ABW) in 28 patients resulted in lower rates of INR achievement (36% vs 68%; $P$ = .006) and using actual body weight with a dosing cap of 100 kg achieved higher rates of reversal.[4] Notably in their analysis, weight and presenting INRs were lower than observed in our analysis, thus the maximum dose of 100 kg was more frequently used in our study. Additionally, Chu and colleagues evaluated use of three-factor PCC (3F-PCC, Profilnine), using a weight-adjusted protocol where patients >90 kg received a fixed dose of 3F-PCC 3000 units. They found that of 45% who did not achieve full reversal (defined as any INR ≥1.5), most were obese with a BMI >30 kg/m$^2$ (41% vs 14%; $P$=.03), along with a higher presenting INR. Both the presenting INR and obesity were related to reversal failure.[15] McKinney and colleagues demonstrated that a fixed-dose strategy of activated PCCs 1000 units for INR ≥5, and 500 units for INR <5 led to lower achievement of INR reversal to 1.4 in obese patients (96% vs 83%; $P$ = .0004).[16]

In this multicenter combined analysis, we observed no difference in achievement of INR ≤1.3, but significantly more patients in the HiWT group achieved an INR ≤1.5. Time to repeat INR was also significantly longer in the HiWT group, perhaps allowing more time for 4F-PCC and vitamin K to take effect (Table 1). Although the nonclinical trial cohort had a significantly longer median time to INR compared to the clinical trial data, this was not found to be clinically significant between groups (124 minutes in LoWT group vs 133 minutes in the HiWT group).

INR achievement in part may also be attributed to the fact that obese patients have more factor VII, fibrinogen, and von Willebrand factor compared to nonobese patients.[13] Notably, in the landmark trial for 4F-PCC, 62% of patients with life-threatening bleeding achieved an INR of ≤1.3 and had a median BMI of 27.6 kg/m$^2$ similar to ours of 26.9 kg/m$^2$ with a 64.2% achievement.[10]

Median doses between groups were different (2132 units vs 2767 units; $P$ < .0001); however, both groups received a similar median weight-based dose of 25 units/kg. This dosing is in line with package insert dosing based on the median presenting INRs (3.21 vs 3.03; $P$ = .36). Although some hypothesize that the obese population requires more than the standard dose for INR reversal, patients in this cohort achieved INR reduction to ≤1.3 at similar rates regardless of bodyweight with similar presenting INRs.

Hemostasis in patients with ICH was not statistically different between groups and was higher than what has been previously published (69%) for patients on warfarin (73% LoWT vs 82% HiWT).[10] Notably in our three centers comprising the nonclinical trial cohort, 80% of patients with ICH achieved an INR ≤1.3, and 93% of patients achieved an INR ≤1.5. Hemostasis did differ for those with GI bleeding (49% vs 89%; $P$ = .003). Many of these patients did not immediately receive cauterization due to scheduling, resource availability, hemodynamic stability, and required transfusion of packed red blood cells while awaiting surgical intervention. This has been documented in the literature as a hindrance to management of patients with GI bleeding.[10,17] Although we did

not collect history of liver disease and location of GI bleed, patients may have had lower rates of hemostasis achievement due to disturbances in coagulation due to underlying liver disease or site of GI bleed, as this may contribute to rebleeding.[18] Notably, in the nonclinical trial cohort of 33 LoWT patients with GIB, the median presenting INR was 4.8 (IQR, 2.8-9.0; range, 1.7-20.1) with 64% of patients achieving INR ≤1.3 and 82% ≤1.5. Of the 11 HiWT patients with GIB, the median presenting INR was 3.1 (IQR, 2.4-4.7; range, 2.2-18.5) and 82% of patients achieved an INR ≤1.3 and 100% ≤1.5. Failure to achieve hemostasis was due to requirement of blood transfusion and requiring a redose of 4F-PCC in one LoWT patient due to continued drop in Hgb and INR <1.5, and one HiWT despite achieving an INR of 1.3.

There was no difference in thrombotic events between groups. Although actual unit dose was higher, dosing and exposure to inactive coagulation factors by units or unit/kg (both were 25 units/kg) was no different between groups; thus, the patients underlying thrombotic risk may have been the driver of the events observed. We did not collect information regarding restart of anticoagulation after reversal or indication for anticoagulation. Mortality was significantly higher in the LoWT group.

There were several limitations to our analysis. This was a retrospective study conducted amongst three institutions that may have had different practice approaches for bleeding related to anticoagulation (including dose rounding and using factor IX component of the PCC vial versus the representative vial size). Although data end points were defined and standardized, all data were collected via an electronic medical health record (EHR). Unfortunately, documentation detail in the EHR varied across institutions, thus limiting our ability to provide additional information surrounding blood product administration. There are notable differences between the inclusion and exclusion criteria between trials as well as the outcomes assessment, including not being a standardized definition as recommended by the ISTH. We included patients within our database without stringent inclusion and exclusion criteria, this data is more generalizable and applicable to real-life practice. Additionally, combining our nonclinical trial data with clinical trial data allowed us to have larger representation of patients in the obese cohort. By including patients from nonclinical trials, we were able to demonstrate real-life use of 4F-PCC compared to a randomized controlled trial with prespecified inclusion criteria. Finally, due to the combination of data, there may have been small differences in definitions of inclusion and exclusion criteria. The time from 4F-PCC administration to follow up INR was different and could have impacted any outcome assessing INR reduction, including the primary outcome. All patient data categories and data collection points were agreed upon by investigator consensus.

## 5 | CONCLUSION

In this large multicenter analysis, we found no difference in achievement of INR ≤1.3 in patients ≤100 kg (LoWT) and >100kg (HiWT). Overall, thrombosis events were similar between the two groups, but hemostasis achievement was higher in the HiWT group.

## ACKNOWLEDGMENTS

Martin L. Lee, PhD, CStat, CSci, FIBMS. Adjunct Professor, Biostatistics, UCLA Fielding School of Public Health. Sheryl Sorourke, Biostatistics. Leo Buckley, PharmD, BCPS Brigham and Women's Hospital, Boston, MA.

## RELATIONSHIP DISCLOSURE

JC is a consultant for Abbott, Anthos Therapeutics, Bristol-Myers Squibb, eXlthera, and Five Prime Therapeutics, and is on the scientific advisory board for Anthos Therapeutics, Bristol-Myers Squibb, eXlthera. Her institution has received research funding from CSL Behring KB previously served on the CSL Behring speaker's bureau. All other authors have nothing to disclose. CSL Behring provided data from the Phase 3b trial and did not provide funding for this study.

## AUTHOR CONTRIBUTIONS

JR contributed to the design of the study and data acquisition and verification, and drafted the manuscript and revisions. KB contributed to the design of the study and data acquisition, and assisted with revisions of the manuscript for important intellectual content. SC contributed to the design of the study and data acquisition, assisted with analysis of the retrospective data, assisted with manuscript editing. CH contributed to the design of the study and data acquisition, assisted with manuscript revisions for intellectual content. KC contributed to the design of the study and data acquisition, and assisted with manuscript editing. LO contributed to the design of the study and revised the manuscript critically for important intellectual content. JMC contributed to the design of the study and revised the manuscript critically for important intellectual content.

## ORCID

*Jessica Rimsans* https://orcid.org/0000-0001-6662-2302
*Jean M. Connors* https://orcid.org/0000-0001-6445-582X

## TWITTER

*Jean M. Connors* @connors_md

## END NOTE

[1]Table 1

## REFERENCES

1. Kcentra® prescribing information. [Accessed 2020 June 17]. Available from http://cslbehring.vo.llnwd.net/o33/u/central/PI/US/Kcentra/EN/Kcentra-Prescribing-Information.pdf
2. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. *Obes Surg*. 2006;16(6):773-776.
3. Klein L, Peters J, Miner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. *Am J Emerg Med*. 2015;33(9):1213-1218.

4. Smetana KS, Ziemba R, May CC, Erdman MJ, Van Matre ET, Jones MG. Adjusted versus actual body weight dosing of 4-factor prothrombin complex concentrate in obese patients with warfarin-associated bleeding. *JJ Thromb Thrombolysis*. 2019;47(3):369-374.
5. Astrup G, Sarangarm P, Burnett A. Fixed dose 4-factor prothrombin complex concentrate for the emergent reversal of warfarin: a retrospective analysis. *J Thromb Thrombolysis*. 2018;45:300-305. doi:10.1007/s11239-017-1586-x
6. Elsamadisi P, Cepeda MAG, Yankama T, Wong A, Tran Q, Eche IM. Weight-based dosing versus a fixed-dose regimen of 4-factor prothrombin complex concentrate in obese patients requiring vitamin K antagonist reversal. *Am J Cardiovasc Drugs*. 2021;21(3):355-361. doi:10.1007/s40256-020-00442-w
7. Dietrich SK, Mixon M, Holowatyj M, et al. Multi-centered evaluation of a novel fixed-dose four-factor prothrombin complex concentrate protocol for warfarin reversal. *Am J Emerg Med*. 2020;38(10):2096-2100. doi:10.1016/j.ajem.2020.06.017
8. Gilbert BW, Morton L, Huffman JB, et al. Modified version of the American College of Cardiology's recommendation for low-dose prothrombin complex concentrate is effective for warfarin reversal. *Am J Emerg Med*. 2020;38(4):806-809. doi:10.1016/j.ajem.2019.12.005
9. Bitonti MT, Rumbarger RL, Absher RK, Curran LM. Prospective evaluation of a fixed-dose 4-factor prothrombin complex concentrate protocol for urgent vitamin K antagonist reversal. *J Emerg Med*. 2020;58(2):324-329. doi:10.1016/j.jemermed.2019.10.013
10. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013;128:1234-1243.
11. Goldstein JN, Refaai MA, Milling TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomized trial. *Lancet*. 2015;385(9982):2077-2087.
12. Luc SA, Whitworth MM, King SE. Effects of obesity on warfarin reversal with vitamin K. *Clin Appl Thromb Hemost*. 2019;25:1076029618824042.
13. Mertens I, Van Gaal LF. Obesity, hemostasis and the fibrinolytic system. *Obes Rev*. 2002;3(2):85-101.
14. Switzer JA, Rocker J, Mohorn P, et al. Clinical experience with three-factor prothrombin complex concentrate to reverse warfarin anticoagulation in intracranial hemorrhage. *Stroke*. 2012;43(9):2500-2502.
15. Chu C, Tokumaru S, Izumi K, Nakagawa K. Obesity increases risk of anticoagulation reversal failure with prothrombin complex concentrate in those with intracranial hemorrhage. *Int J Neurosci*. 2016;126(1):62-66.
16. Tomaselli G, Mahaffey K, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. *J Am Coll Cardiol*. 2017;70(24):3042-3067.
17. Refaai MA, Kothari TH, Straub S, et al. Four-factor prothrombin complex concentrate reduces time to procedure in vitamin K antagonist-treated patients experiencing gastrointestinal bleeding: a post hoc analysis of two randomized controlled trials. *Emerg Med Int*. 2017;2017:8024356. doi:10.1155/2017/8024356
18. Rodrigues A, Carrilho A, Almeida N, et al. Interventional algorithm in gastrointestinal bleeding—an expert consensus multimodal approach based on a multidisciplinary team. *Clin Appl Thromb Hemost*. 2020;26:1076029620931943. doi:10.1177/1076029620931943


## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Rimsans J, Berger K, Culbreth S, et al. Comparison of 4F-PCC in obese and nonobese patients with life-threatening bleeding or requiring emergent surgery. *Res Pract Thromb Haemost*. 2021;5:e12624. doi:10.1002/rth2.12624